Discussion

59O - Targeting CDK4/6 in Her2 Positive Breast Cancer: Therapeutic Effect, Markers, and Combination Strategies

65O - Generation of mouse models for the identification of new driver pathways of drug resistance in human breast cancer

Dr Nicholas Turner

The Royal Marsden NHS Foundation Trust

NHS

ICR The Institute of Cancer Research

Disclosure relevant to presentation

Nicholas Turner

I have received honoraria from Pfizer, Novartis

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

Targeting CDK4/6 in Her2 Positive Breast Cancer

Therapeutic Effect, Markers, and Combination Strategies

Agnieszka Witkiewicz and Erik Knudsen

Derek Cox

Jorge Franco

Uthra Balaji

Barbara Haley

UT SOUTHWESTERN MEDICAL CENTER

Abstract CT101

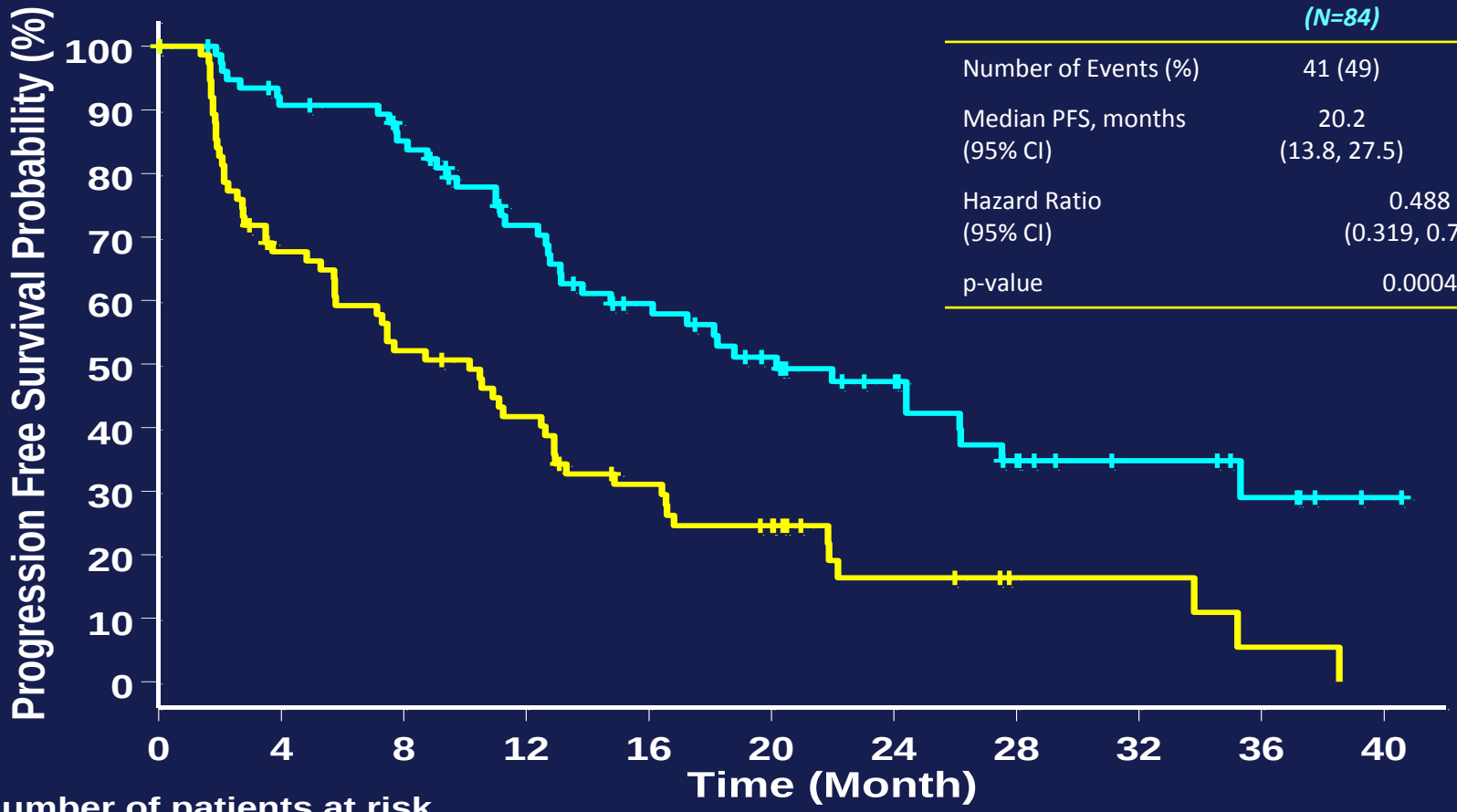
Final Results of a Randomized Phase 2 Study of Palbociclib (PD 0332991) a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (PALOMA-1/TRIO-18)

RS Finn,[1] JP Crown,[2] I Lang,[3] K Boer,[4] IM Bondarenko,[5] SO Kulyk,[6] J Ettl,[7] R Patel,[8] T Pinter,[9] M Schmidt,[10] Y Shparyk,[11] AR Thummala,[12] NL Voytko,[13] X Huang,[14] ST Kim,[14] S Randolph,[14] DJ Slamon[1]

[1]University of California Los Angeles, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]Orszagos Onkologiai Intezet, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]University Hospital Mainz, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Henderson, NV, USA; [13]Kyiv City Clinical Oncology Center, Ukraine; [14]Pfizer Oncology, San Diego, CA, USA

Presented at AACR 2014; April 6, 2014; San Diego, CA USA

Progression-Free Survival (ITT)



	PAL + LET (N=84)	*LET (N=81)*
Number of Events (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)
Hazard Ratio (95% CI)	0.488 (0.319, 0.748)	
p-value	0.0004	

Palbociclib efficacy in ER positive HER2 negative breast cancer

Finn *et al* AACR 2014

articles

Specific protection against breast cancers by cyclin D1 ablation

Qunyan Yu, Yan Geng & Piotr Sicinski

Department of Cancer Biology, Dana-Farber Cancer Institute, and Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115, USA

DOI: 10.1093/jnci/djs002
Advance Access publication on February 1, 2012.

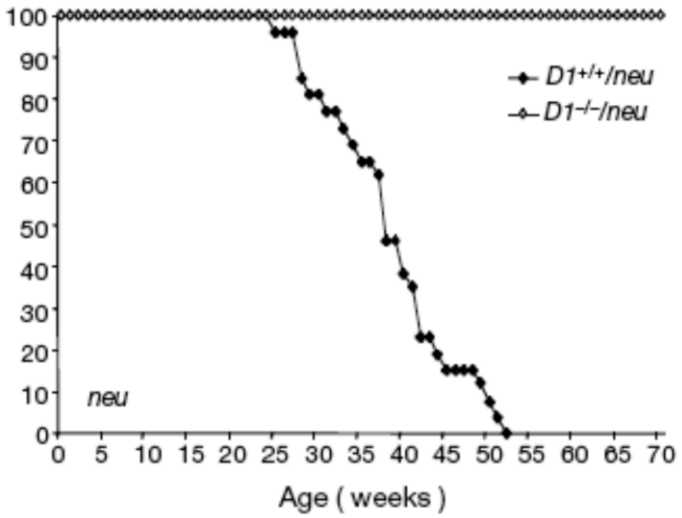
ARTICLE

Multiple Roles of Cyclin-Dependent Kinase 4/6 Inhibitors in Cancer Therapy

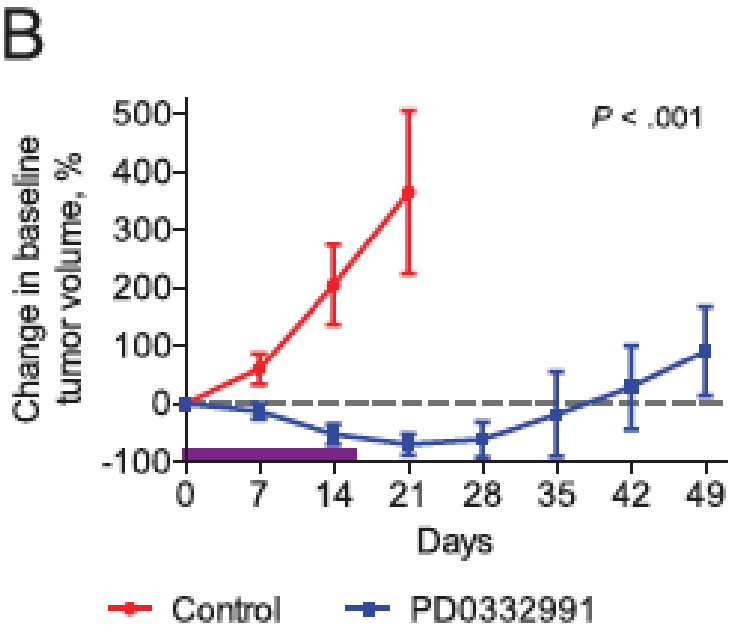
Patrick J. Roberts, John E. Bisi, Jay C. Strum, Austin J. Combest, David B. Darr, Jerry E. Usary, William C. Zamboni, Kwok-Kin Wong, Charles M. Perou, Norman E. Sharpless

Manuscript received May 4, 2011; revised December 13, 2011; accepted December 28, 2011.

Loss of cyclin D1 protects against MMTV - HER2 driven oncogenesis



Similar model is highly sensitive to palbociclib

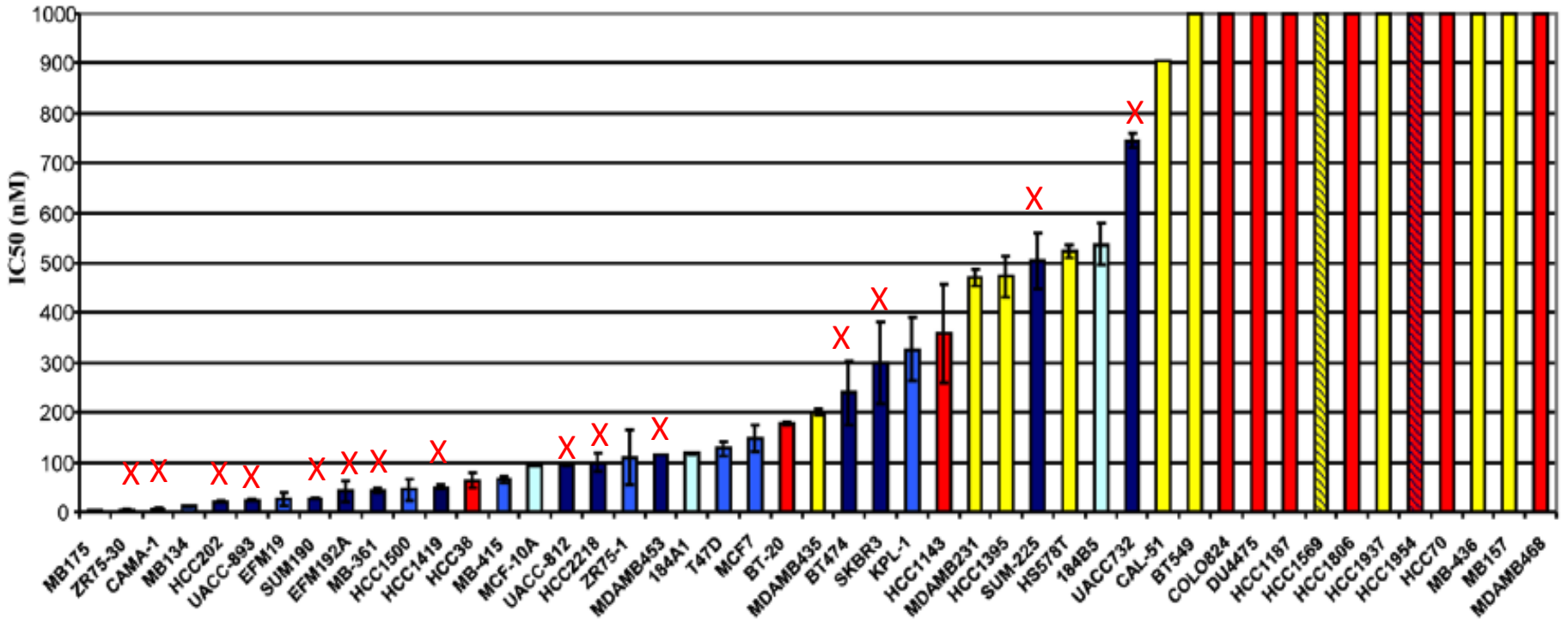


Yu *et al* Nature 2001

Roberts *et al* JNCI 2012

Sensitivity to CDK4/6 inhibition Luminal vs non-luminal

Figure 1



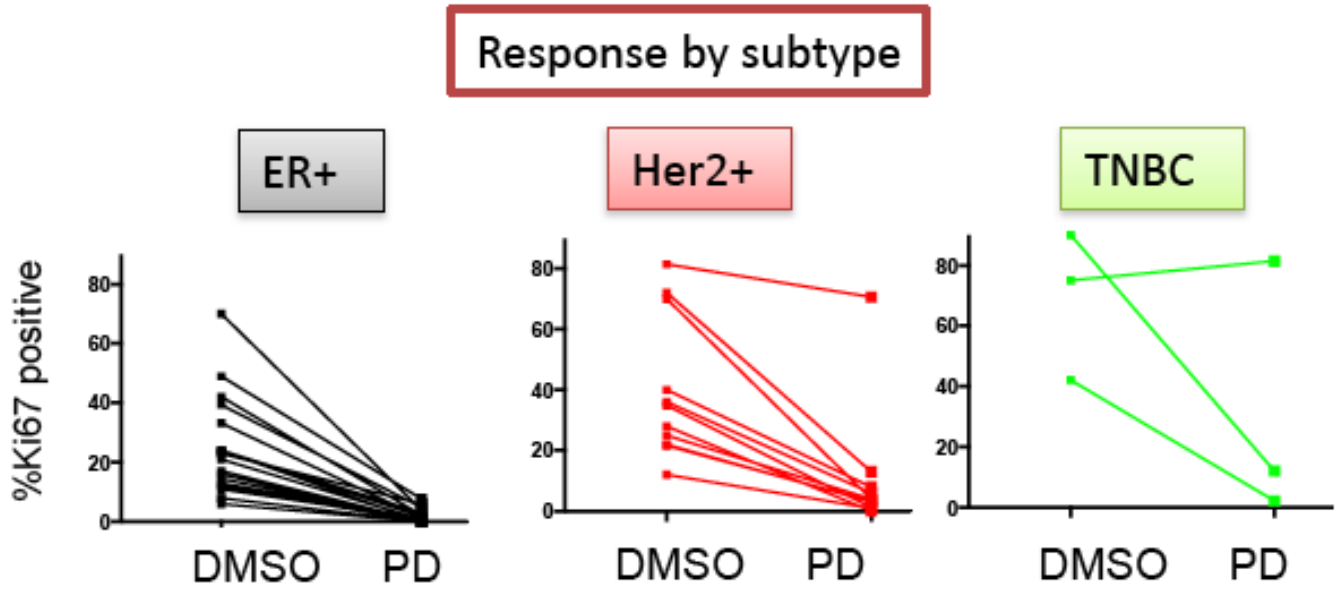
Subtype

- Luminal
- HER2 amplified
- Immortalized
- Non-luminal/post EMT
- Non-luminal

HER2 pos ER positive and negative sensitive

Finn RS, *et al*. Breast Cancer Res 2009.

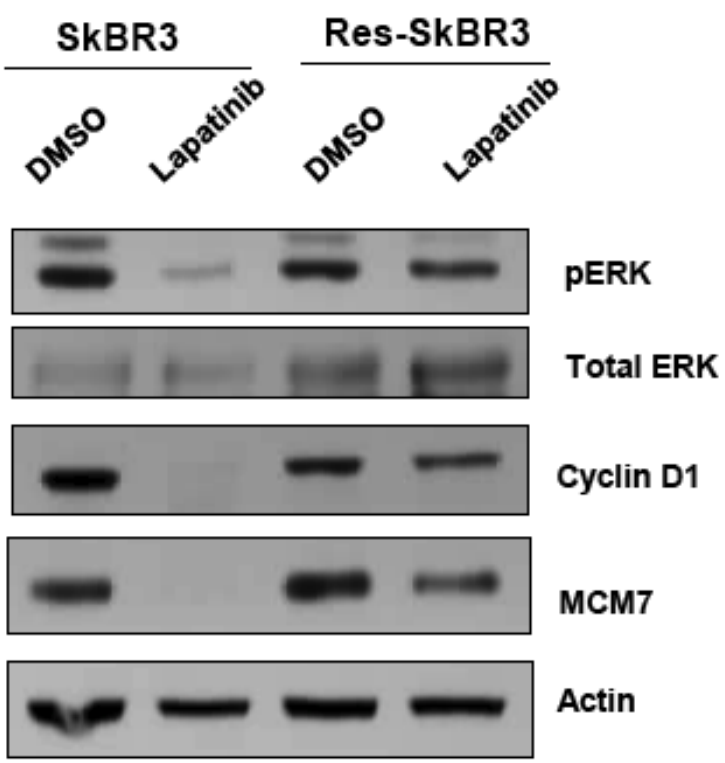
Explants to study the effects of Palbociclib

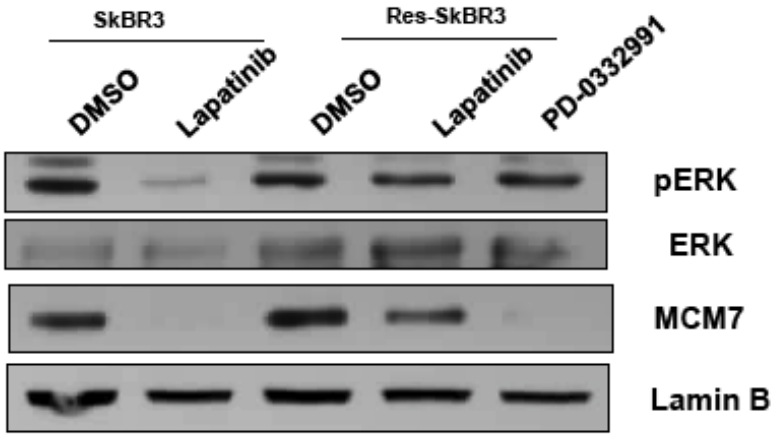


HER2 positive explants are sensitive to CDK4/6 inhibiton

TNBC
- Many TNBC cell lines resistant, an effect of small numbers?
- Luminal-like TNBC

HER2 signalling promotes cell proliferation through D type cyclins





Questions for CDK4/6 inhibitor development

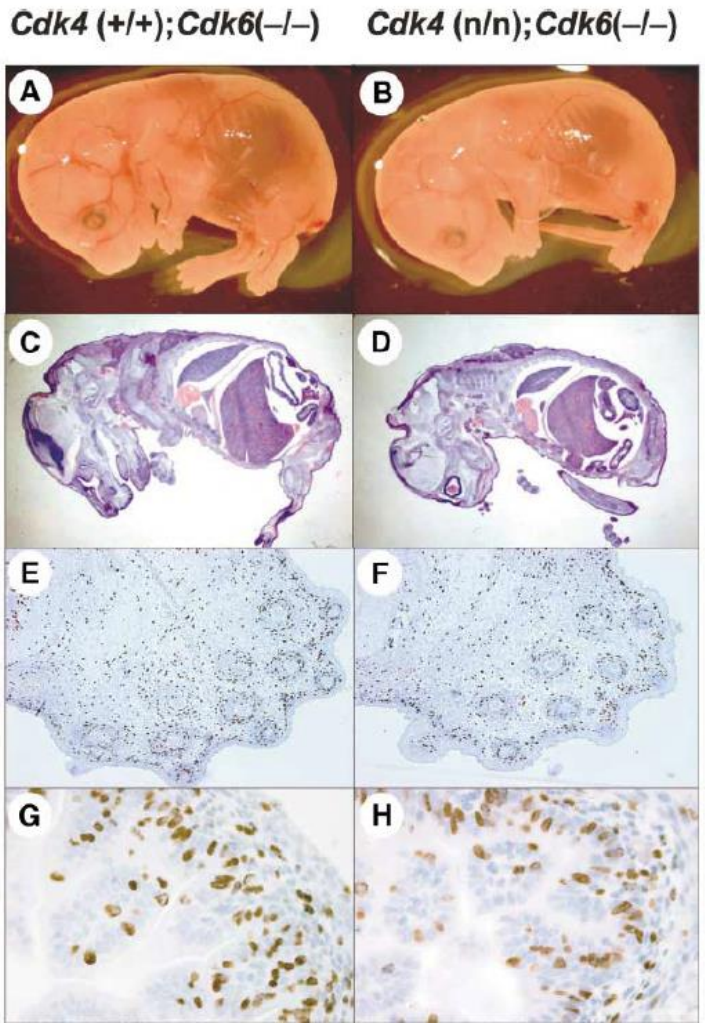
- Therapeutic window for CDK4/6 inhibitors
- Single agent or combinations?
- What are the mechanisms of resistance?

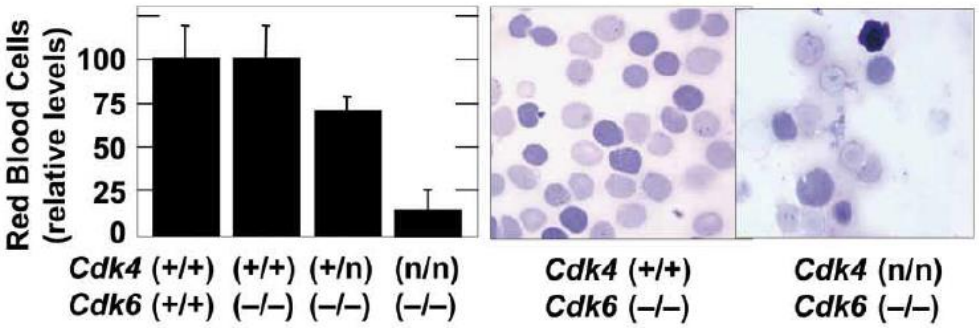
Cell, Vol. 118, 493–504, August 20, 2004, Copyright ©2004 by Cell Press

Mammalian Cells Cycle without the D-Type Cyclin-Dependent Kinases Cdk4 and Cdk6

Mouse embryos morphologically normal

Embryos die in late gestation of anaemia





Only specific cell types need CDK4/6 for proliferation

Malumbres et al Cell 2004

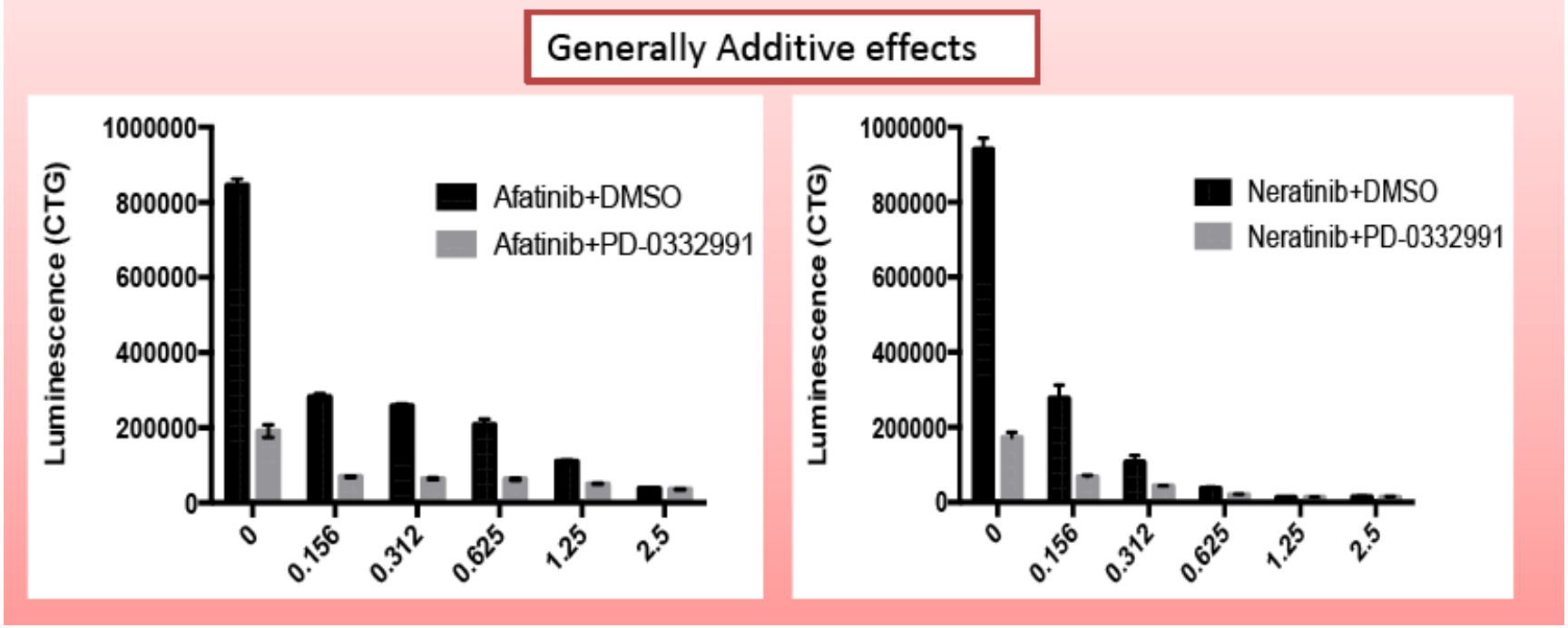
Most Common All-Causality AEs ≥15% (AT)

	PAL + LET (N=83)			LET (N=77)		
	G1/2 (%)	G3 (%)	G4 (%)	G1/2 (%)	G3 (%)	G4 (%)
Neutropenia	20	48	6	4	1	0
Leukopenia	24	19	0	3	0	0
Fatigue	36	2	2	20	1	0
Anemia	29	5	1	5	1	0
Nausea	23	2	0	12	1	0
Arthralgia	22	1	0	13	3	0
Alopecia	22	0	0	3	0	0
Diarrhea	17	4	0	10	0	0
Hot flush	20	0	0	12	0	0
Thrombocytopenia	14	2	0	1	0	0
Decreased appetite	14	1	0	6	0	0
Dyspnea	13	2	0	6	1	0
Nasopharyngitis	16	0	0	10	0	0
Back pain	13	0	1	14	1	0

AT=As Treated Population

Finn *et al* AACR 2014

Combination therapy with CDK4/6 inhibitors

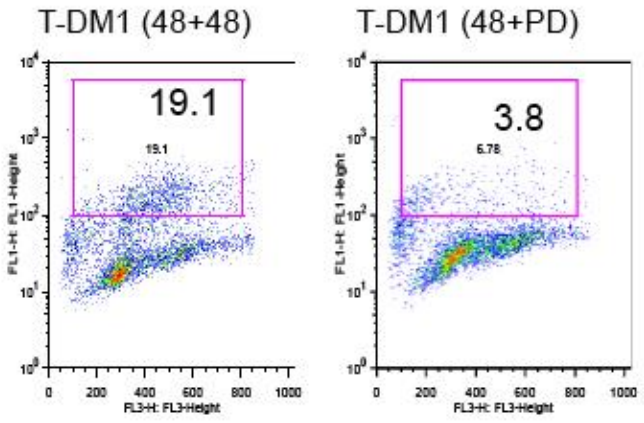


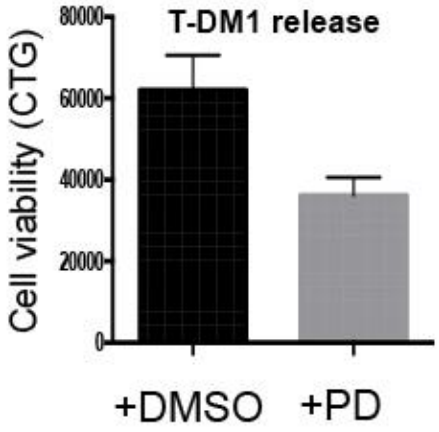
Vertical combination effects

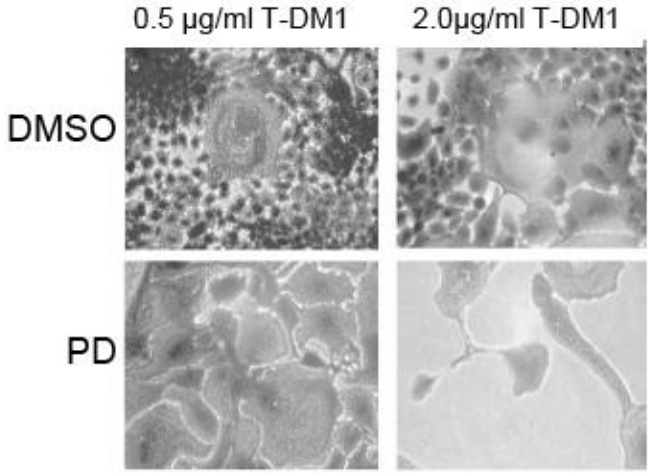
Limited toxicity profile of CDK4/6 inhibitors may make them highly suitable for targeted therapy combinations

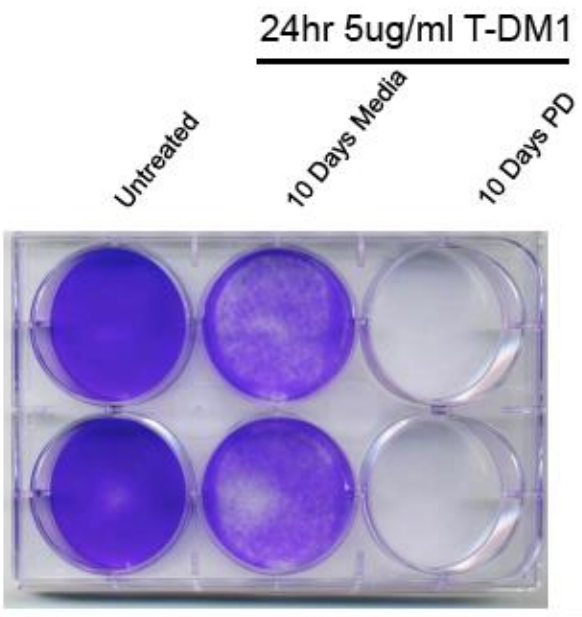
CDK4/6 inhibition can augment T-DM1 activity

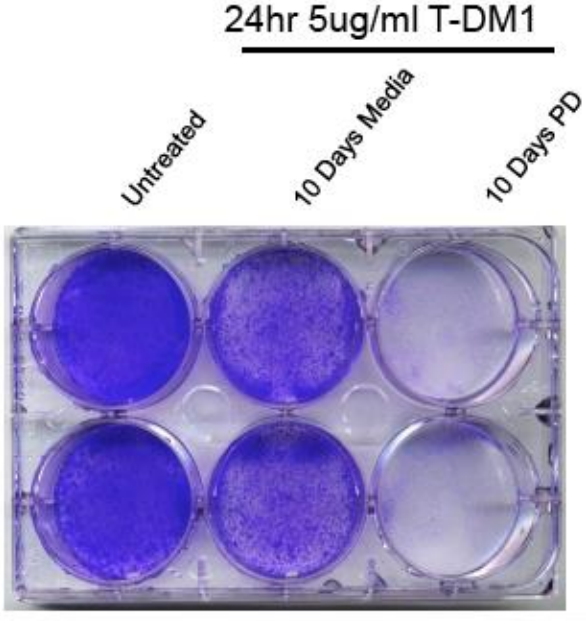
Prevents growth of residual cells





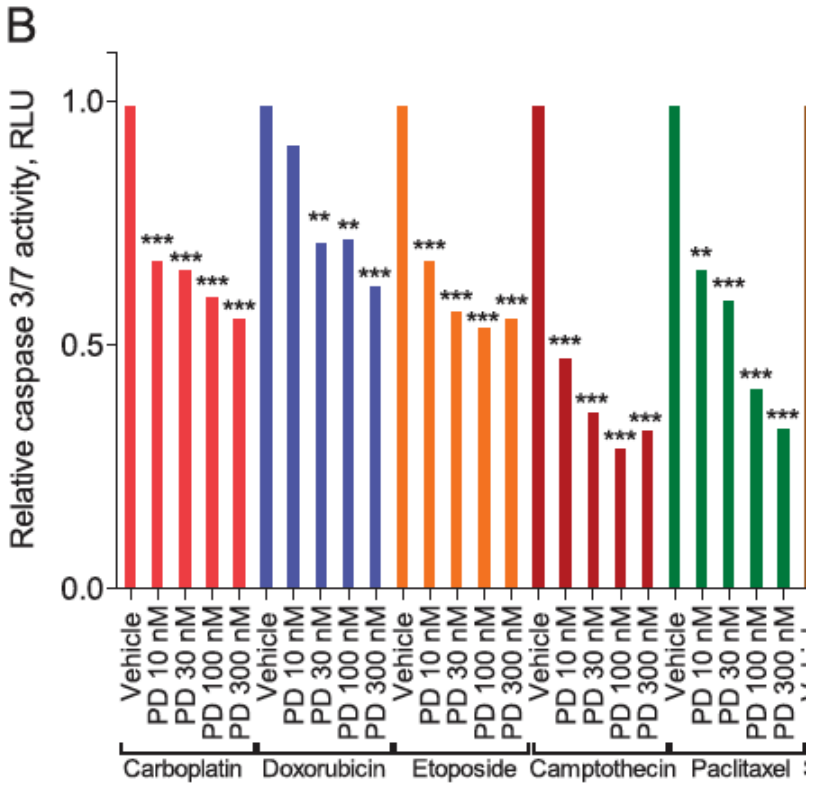






Palbociclib pretreatment induces resistance to chemotherapy

Inhibition of apoptosis in an Rb wildtype cell lines

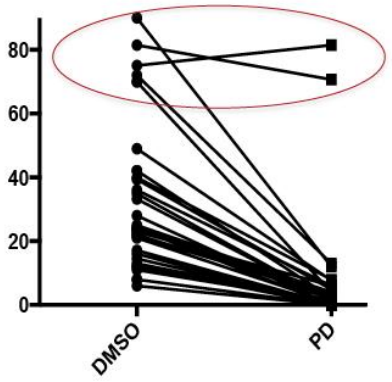


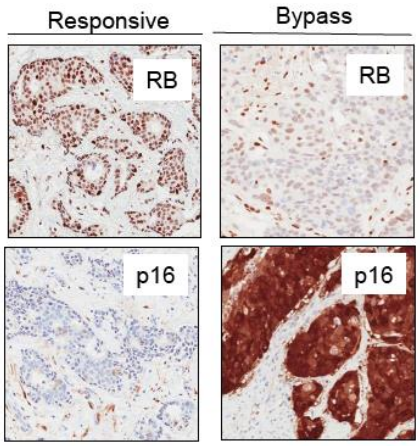
Very careful scheduling is required for combinations with CDK4/6 inhibition and chemotherapy to prevent antagonism

Roberts *et al* JNCI 2012

Mechanisms of resistance

Loss of RB





Lack of dependence CDK4/6?

What determines whether cell types are dependent on CDK4/6?

- many basal-like cancers may not be dependent on CDK4/6

Mechanisms of acquired resistance?

Generation of mouse models for the identification of new driver pathways of drug resistance in human breast cancer

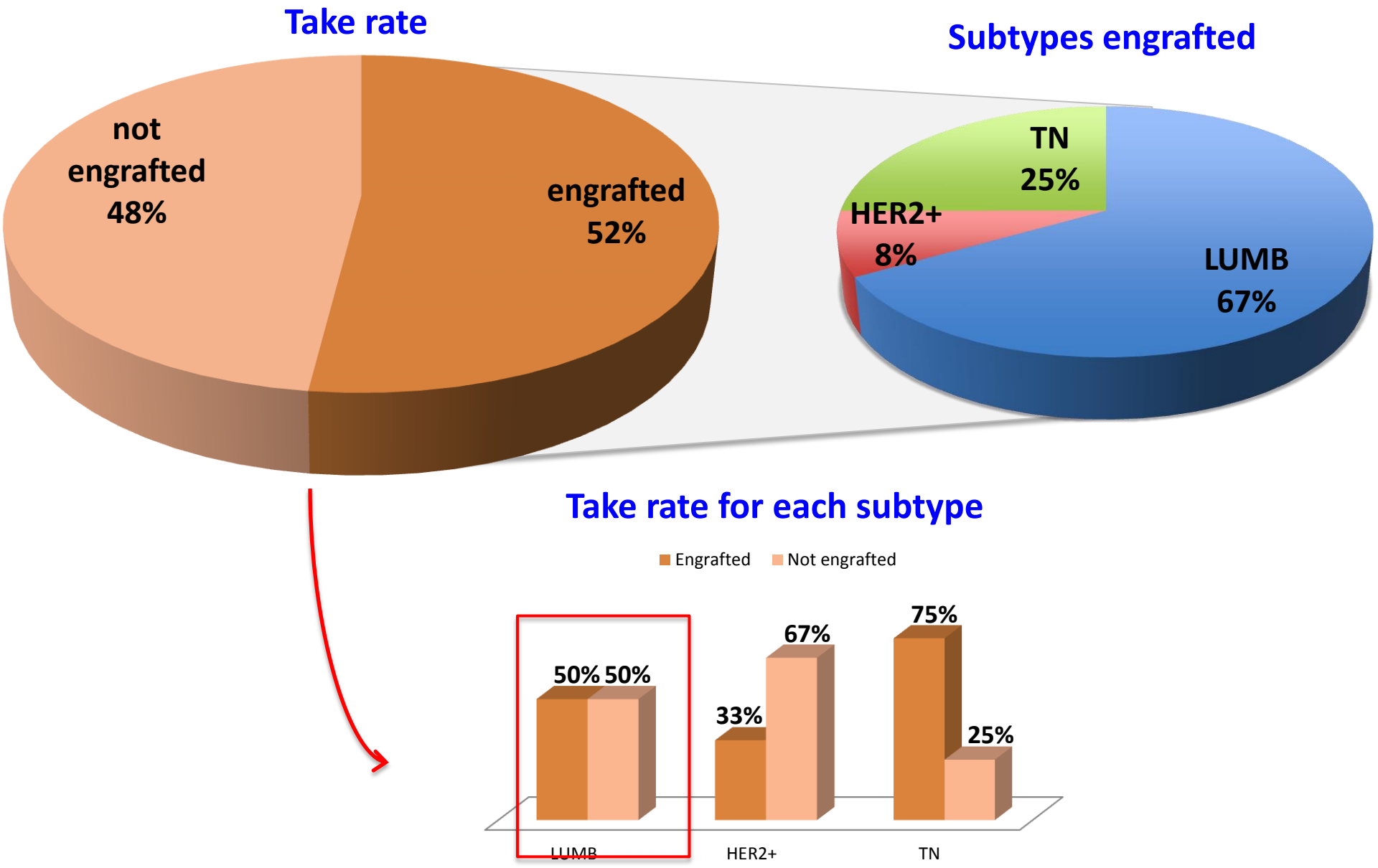
Patient derived xenografts

- Drug sensitivity and resistance testing
- Combination therapy exploration
  - Discussed in great detail today

Patient derived xenografts

- Drug sensitivity and resistance testing
- Combination therapy exploration
- *In vivo* target discovery

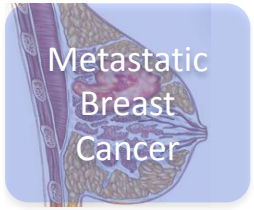
Grafting metasatic samples improves take rate of ER positive samples

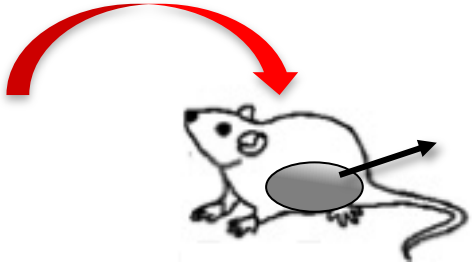


shRNA screen

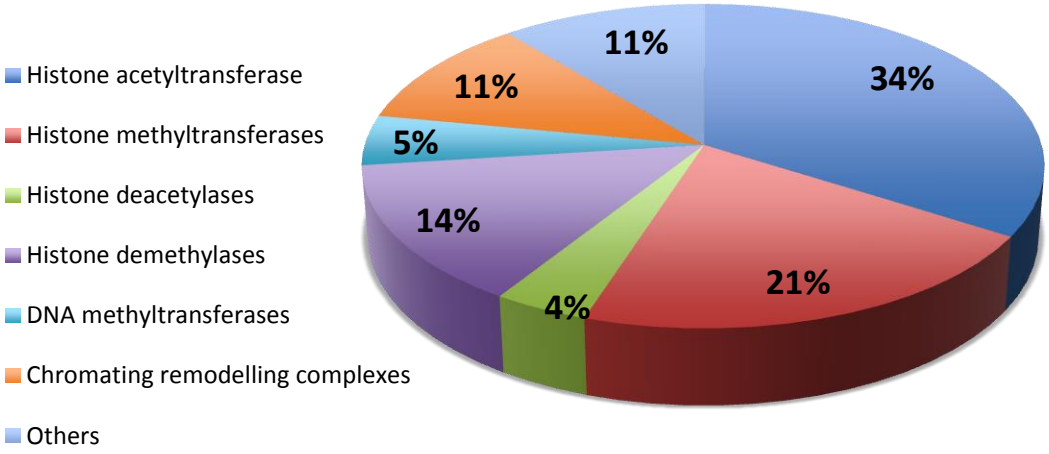
Cellecta Barcoded hEPI Library

(237genes/2410 shRNAs)





Library choice: druggable genes involved in tumor take and growth



Melanoma shRNA screening:

1. ***Choice of depleted top genes***
2. ***In vivo and in vitro validation***

Relevant for breast carcinoma

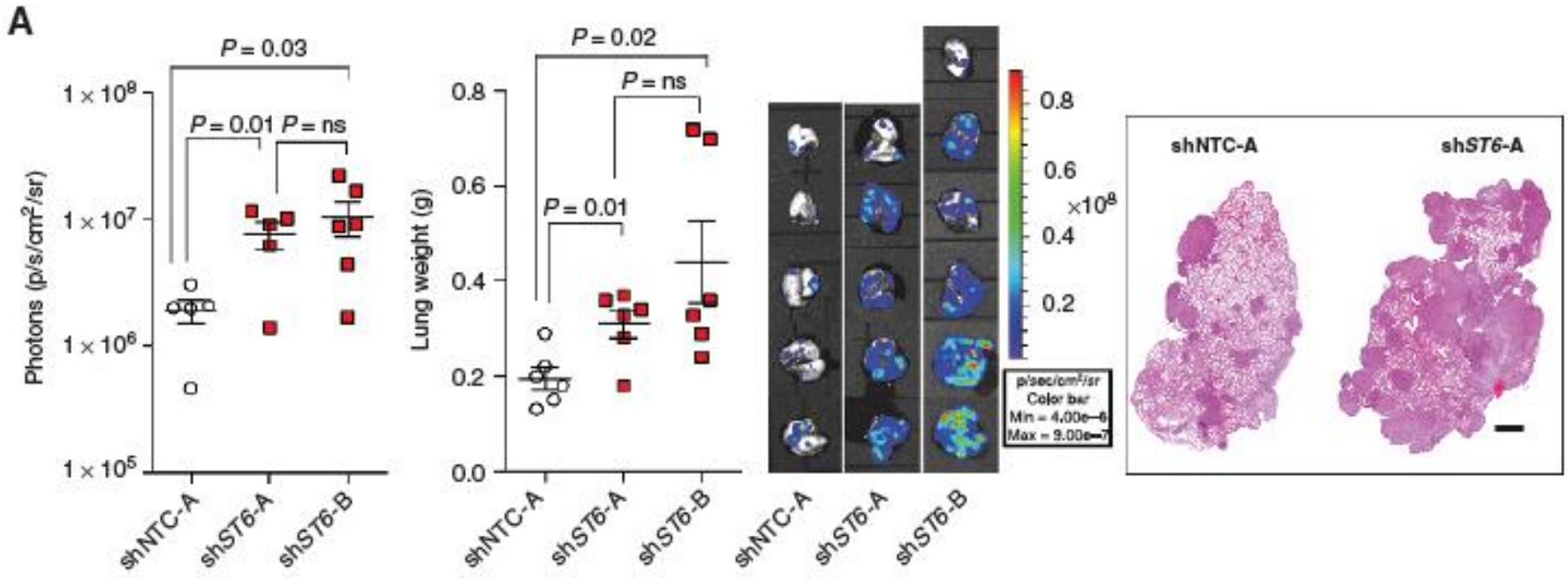
Identification of novel druggable hits

CANCER DISCOVERY

An *In Vivo* Functional Screen Identifies ST6GalNAc2 Sialyltransferase as a Breast Cancer Metastasis Suppressor

Nirupa Murugaesu, Marjan Iravani, Antoinette van Weverwijk, et al.

Cancer Discovery 2014;4:304-317. Published OnlineFirst February 11, 2014.

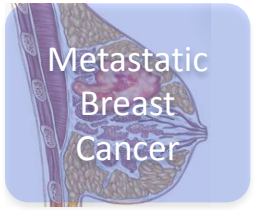


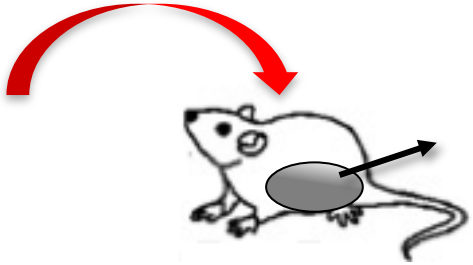
Murugaesu et al Cancer Discov 2014

shRNA screen

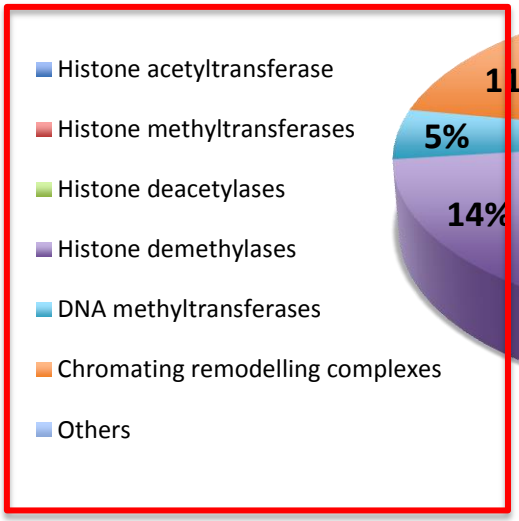
Cellecta Barcoded hEPI Library

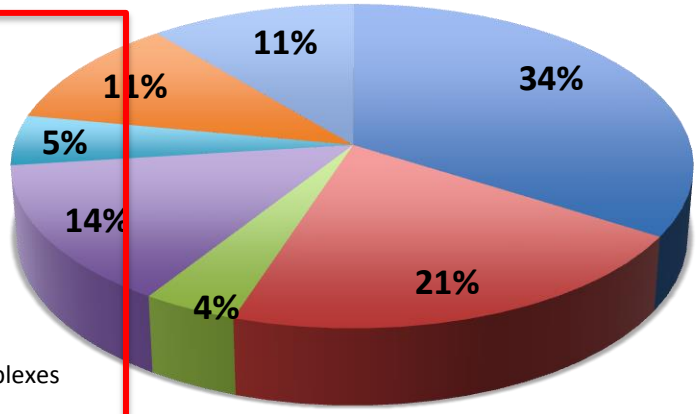
(237genes/2410 shRNAs)





Library choice: druggable genes involved in tumor take and growth





Screens to study tumour-stromal interactions, paracrine signalling, metastasis